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Potential role of selection bias in the association between childhood leukemia and residential magnetic fields exposure: A population-based assessment

Danna A. Slusky [a,*], Monique Does [a], Catherine Metayer [a], Gabor Mezei [b], Steve Selvin [a], Patricia A. Buffler [a,1]

[a] School of Public Health, University of California, Berkeley, CA, United States
[b] Electric Power Research Institute, Palo Alto, CA, United States

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ABSTRACT

Purpose: Data from the Northern California Childhood Leukemia Study (NCCLS) were used to assess whether selection bias may explain the association between residential magnetic fields (assessed by wire codes) and childhood leukemia as previously observed in case–control studies.
Methods: Wiring codes were calculated for participating cases, $n = 310$; and non-participating cases, $n = 66$; as well as for three control groups: first-choice participating, $n = 174$; first-choice non-participating, $n = 252$; and replacement (non-first choice participating controls), $n = 220$.
Results: Participating controls tended to be of higher socioeconomic status than non-participating controls, and lower socioeconomic status was related to higher wire-codes. The odds ratio (OR) for developing childhood leukemia associated with high wire-codes was 1.18 (95% CI: 0.85, 1.64) when all cases were compared to all first-choice controls (participating and non-participating). The OR for developing childhood leukemia in the high current category was 1.43 (95% CI: 0.91, 2.26) when participating cases were compared to first-choice participating controls, but no associations were observed when participating cases were compared to non-participating controls (OR = 1.06, 95% CI: 0.71, 1.57) or to replacement controls (OR = 1.06, 95% CI: 0.71, 1.60).
Conclusions: The observed risk estimates vary by type of control group, and no statistically significant association between wire codes and childhood leukemia is observed in the California population participating in the NCCLS.

1. Introduction

The association between extremely low-frequency (ELF) magnetic fields (MF) and childhood leukemia has been extensively studied since the first publication of a case–control study by Wertheimer and Leeper [1], which used residential wire configuration codes (wire codes) as a surrogate for magnetic fields. Since this initial study, more than 30 epidemiological studies have been conducted, with improvements in assessment of magnetic fields by using calculated and directly measured fields. The results of the wire code studies have not been consistent, with several studies indicating a positive association between childhood leukemia and magnetic field exposures (assessed by wire codes) [1–4] while others showing no association [5,6]. Most of these studies were included in two pooled analyses published in 2000 by Greenland et al. [7] and Ahlbom et al. [8], including original data from 15 and nine studies, respectively. Greenland et al. found no association between childhood leukemia and MF levels less than 0.3 μT, but reported a statistically significant 1.7 fold increased risk for MF levels over 0.3 μT (95% CI: 1.2, 2.3), compared to a reference value of less than 0.1 μT. The second pooled analysis, by Ahlbom et al., indicated a summary odds ratio of 2.0 (95% CI: 1.3, 3.1) for exposure >0.4 μT as compared with exposure <0.1 μT [8]. Following these two pooled analysis in 2002, the International Agency for Research on Cancer classified power-frequency magnetic fields as a possible human carcinogen (group 2B) [9].

In 2010, Kheifets et al. published the results of a subsequent pooled analysis using seven studies on residential magnetic fields

* Corresponding author at: Division of Epidemiology, UC Berkeley School of Public Health, 1995 University Avenue, Suite 460, Berkeley, CA 94704, United States. Fax: +1 510 643 1735.
E-mail address: dannaaharon@gmail.com (D.A. Slusky).
[1] Author deceased.

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and childhood leukemia that were published after 2000. The results were consistent with the previous pooled analyses with 1.4 fold increased risk for MF levels ≥0.3 μT (95% CI: 0.9, 2.4) [10]. A recent California-based case–control study by Does et al. found no association of childhood leukemia with measured magnetic fields or household contact currents [11,12], a hypothesized potential confounder of the magnetic field-leukemia association.

In spite of suggestive epidemiologic findings, there is no biological evidence from either cellular or animal studies to support the plausibility of the epidemiologic observations. Hence, it remains uncertain whether a causal association between childhood leukemia and MF exists. Among alternative explanations for the observed associations are the role of confounding factors, measurement errors, and selection bias.

Confounding effects of socioeconomic status (SES), residential mobility, residence type, social contacts, traffic density, and household contact currents have been raised as possible explanations for the observed associations [13–16]. However, despite extensive research, to date, no single confounder or set of confounders has been identified that could explain the observed association [14,17].

Selection bias has been suggested as a potential explanation in several studies [18]. An adequate assessment of selection bias, however, requires considerable additional resources as well as modifications in study design and has been difficult to conduct in most studies. To our knowledge, only three studies have attempted to assess the role of selection bias in the association between childhood leukemia and MF.

Gurney et al. assessed the relationship between family income and wire codes and noted that lower family income tended to be associated with the higher wire codes category [15]. Subsequently, Mezei et al. evaluated the role of control non-participation and the potential for selection bias in the 1999 Canadian case–control study of childhood leukemia and residential magnetic field exposure [6,19]. These authors indicated that the first-choice non-participating controls tended to be of lower SES than the replacement controls, and that lower SES was related to higher wire code categories [19]. Consistent with the report by Hatch et al. regarding the impact of participation on risk estimates [14], Mezei et al. reported that the risk estimates for childhood leukemia in the highest exposure category were 1.6 (95% CI: 1.0, 2.6) when the actual participant controls (first-choice and non-first choice) were used, and 1.3 (95% CI: 0.8, 2.1) when all first-choice controls were used [19].

The aim of our study is to further assess whether selection bias may explain the observed epidemiologic association between magnetic fields and childhood leukemia as noted in previous studies by using residential information and wire code measurements for both participating and non-participating cases as well as controls. Because birth certificates were used in the control selection process, the NCCLS offers a rare opportunity to evaluate demographic characteristics and wire codes for a large number of non-participating and participating leukemia cases and controls.

2. Materials and methods

2.1. Study population

The study population is a subset of the Northern California Childhood Leukemia Study, a case–control study of childhood leukemia in 35 northern and central California counties (1995–present) for whom residential wire codes could be determined. Cases with newly diagnosed leukemia are recruited from nine hospitals, usually within 72 h of diagnosis.

The eligibility criteria for cases and controls of the parent study were: (1) residence in the study area; (2) age less than 15 years of age at the time of case diagnosis (reference date for controls); (3) no previous diagnosis of cancer; and (4) availability of at least one English or Spanish speaking parent or guardian. The wire code study conducted from 2002 to 2007 includes all NCCLS eligible subjects who were ascertained for the parent study from 1995 to 2006, regardless of their actual participation in the parent study. In addition, wire code study subjects were required to be born in the study area, have a valid residential California address (from birth certificate), and be less than 8 years of age at the time of case diagnosis (reference date for control). Cases and controls excluded from the NCCLS due to language were included in the wire code study if they met all other eligibility criteria (Fig. 1).

A detailed description of control selection in the parent NCCLS was previously published [20–23]. Briefly, for each case, four potential controls were randomly selected from birth certificates from the California Office of Vital Records, matched on age, gender, Hispanic ethnicity, and maternal race [21]. One of the four birth certificate controls was randomly selected as the first potential control to be recruited for the study (referred to as ideal controls [A]). Professional interviewers contacted each family using standardized searching protocols. If the first-choice control was found to be eligible and agreed to participate he/she was classified as a first-choice participating control [B]. If the first-choice control could not be located, was ineligible, or declined to participate he/she was classified as a first-choice non-participating controls [C], and the next randomly selected potential control was pursued. This procedure was repeated until an eligible and consenting non-first choice control was enrolled in the study, and these were classified as participating replacement controls [D]. If no control was enrolled by using the first set of four birth certificates, additional certificates were requested from the Center for Health Statistics and the process described above was repeated.

The process of case and control selection for the wire-code study is presented in Fig. 1. For these analyses, ideal cases include all participating (n = 310) and non-participating (n = 66) cases. The controls were divided into two groups. Ideal controls [A] consisted of all first-choice controls [B + C], n = 426 (participating [B]; n = 174, and non-participating [C]; n = 252). The second group of actual controls [E], consisted of all participating controls [B + D], n = 394 (first-choice participating controls [B]; n = 174, and the participating replacement controls (non-first choice participating) [D]; n = 220).

The study was approved by the University of California Committee for the Protection of Human Subjects, the California Health and Human Services Agency Committee for the Protection of Human Subjects, and the Institutional Review Boards of all the participant hospitals.

2.2. Data collection

Socio-demographic and residential address data were collected from birth certificates for all cases and controls, regardless of their participation status. Birth residences were assigned address-level latitude and longitude coordinates using a geographic information system (GIS). Each address was assigned to a 1990 or 2000 US Census block group, depending on the child's date of birth. The geocoding was carried out using ArcView GIS software [24]. Data from the U.S. Census Bureau were used to derive neighborhood measures of urbanization and SES. The methods for creating these variables have been previously described [25,26]. In short, urbanization included three levels: large metro, city, and rural/town. To create the SES neighborhood variables, the California block groups were ranked separately by education, income, and occupation according to quartiles, based on the statewide adult population [27,28].